Remarks

Claim 4 has been canceled without prejudice to its prosecution at another time and new claim 18 has been added. Claims 1-3, 5-10 and 12-18 are therefore pending in this application.

The term "viral vaccine" in claims 1 and 5 has been deleted and replaced with "virus." Support for this subject matter can be found throughout the specification as originally filed, for example, at page 6, line 9 to page 9, line 22 and in the Examples. The gene product names in claims 1 and 14-17 have also been capitalized.

Support for new claim 18 can be found throughout the specification and claims as originally filed. For example, support for the subject matter of claim 18 can be found in original claim 1 and in the Examples (see also FIGs. 1 and 8).

Applicant submits that these amendments add no new matter.

Claim Objections

The Examiner has objected to claim language relating to gene product names, alleging that gene product names should be capitalized and that gene names are italicized. Applicant submits that the claim language without amendment is clear and definite however gene product names have been capitalized in the claims. Applicant submits that no new matter has been added to the application and requests withdrawal of this objection to the claims.

35 U.S.C. § 112, First Paragraph, Rejection

Claims 1-3, 5-10 and 12-17 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. The Examiner has alleged the invention lacks working examples and a teaching on how to overcome the alleged well known difficulties in the field of HIV-1 vaccine development.

Applicant submits that the claims do not recite the term "vaccine." Instead, claim 1 is directed to a method of stimulating a HIV1-specific $CD8^+$ response in a human infected with an HIV retrovirus said method comprising: administering to the human, a recombinant virus, which enters the cells of the human and intracellularly produces HIV specific peptides for presentation on the cell's MHC class I molecules, where said peptides are presented in an amount sufficient to stimulate a protective $CD8^+$ HIV structural antigen response, and where said human (i) has a

viral load of less than 10,000 viral copies per ml of plasma and a $CD4^+$ cell count of above 500 cells/ml, and (ii) has been treated with one or more anti-viral agents, which contributed to a lower viral copy and higher $CD4^+$ cell count than before treatment, where said HIV specific peptides comprise HIV Gag, Gp120, Nef or Pol peptides.

In particular, the inventors have recognized that after HIV infection, the available anti-retroviral treatment regimens can sufficiently restore the patient's immune system to permit the patient to mount a HIV1-specific $CD8^+$ response when the patient is provided with a $CD8^+$-inducing composition that includes a recombinant virus that can express HIV-specific peptides. Thus, claims to stimulating a HIV1-specific $CD8^+$ response in a human infected with an HIV retrovirus are enabled. Further comments are provided below illustrating that one of skill in the art can readily make and use the invention.

Correlates of Human Protection

The Examiner first alleges that the disclosure fails to provide guidance as to the specificity and titer of the immune response. Applicant submits that while the invention can result in reduced HIV viral titers and increased anti-HIV antibody titers in human treated with the present methods, the claims are not explicitly directed to reducing viral titers or increasing antibody titers in the human. Applicant can describe his or her invention as he or she chooses. Thus, Applicant reminds that Examiner that Applicant reminds the Examiner that the rejected claims are directed to *stimulating a HIV1-specific $CD8^+$ response.*

Accordingly, with regard to the specificity of the response, the claim language explicitly states that the response is HIV1-specific. Moreover, the claim explicitly lists what types of HIV peptides to use (Gag, Gp120, Nef or Pol peptides) to obtain such an HIV1-specific response.

With regard to the allegations as to the titer of the immune response, the rejected claims are directed to *stimulating a $CD8^+$ response*, meaning that the $CD8^+$ response in the human treated is *increased.* As is known to one of skill in the art, pre-treatment HIV1-specific $CD8^+$ levels can vary from one human to another. As defined by the specification at page 4, lines 7-9, an efficient $CD8^+$ response refers to the ability of cytotoxic $CD8^+$ T cells to recognize and kill cells expressing foreign peptides. Therefore, in the context of stimulating a $CD8^+$ response achieving a specific "titer" does not make sense because the invention is directed to increasing

the ability of cytotoxic $CD8^+$ T cells to recognize and kill cells expressing foreign (i.e. HIV1) peptides, no matter what the pre-treatment $CD8^+$ level.

Applicant further submits that $CD8^+$ responses are not necessarily measured by titer and that other methods may be more accurate for assessing whether $CD8^+$ response has been stimulated. The specification describes such methods at page 14, line 22 to page 15, line 9 (and in the Examples). Such methods can involve, for example, tetramer staining pf PBMCs, interferon release or cytotoxicity assays. Accordingly, the specification and claims specifically explain set forth a new method for stimulating a HIV1-specific $CD8^+$ response and describe how to measure such HIV1-specific $CD8^+$ responses so that one of skill in the art will know whether it has been stimulated or not. Applicant submits that nothing more is needed.

Vaccine Failure due to Quasispecies Nature of HIV

The Examiner has second alleged that HIV vaccines frequently fail because of the quasispecies nature of HIV infection. Applicant requests that the Examiner note that, rather than being directed to a vaccine composition, the claims are directed to administration of a recombinant virus where, after administration, the virus intracellularly produces HIV specific peptides and thereby stimulates an HIV1-specific $CD8^+$ response in a human. Such stimulation provides a therapeutic benefit whether or not the HIV infection is eradicated and whether or not the stimulation is transient. Accordingly, the alleged quasispecies nature of HIV is immaterial to the enable of the present claims.

Moreover, as shown by Smith et al., priming with an HIV-1 clade B DNA followed by MVA boosting, where the DNA and MVA encoded gag, pol and/or env proteins, did elicit CD8+ T cell responses and those CD8+ T cell responses recognized another HIV-1 clade (A/G). *See* Smith et al. AIDS Res. Human Retrovir. 21: 140-144 (2005) (submitted in a May 2005 Information Disclosure Statement). Hence, HIV1 peptides from a variety of HIV-1 strains or clades can stimulate an HIV1-specific CD8+ response even when the animal or patient becomes exposed to a new variety, strain or clade of HIV-1

Immunogens

The Examiner has alleged that the specification does not provide sufficient guidance as to the immunogens employed. Applicants need not describe every nuance of the invention in order to satisfy the requirements of 35 U.S.C. § 112. In particular, that which is known need not be described in the application. For example, sequences for HIV peptides and nucleic acids, for example, Gag, Pol, Pro, Tat, Nef, Rev, Vif, Vpr and Env peptides and nucleic acids are publicly available and need not be listed in the application. At the time of filing, one of skill in the art could readily insert nucleic acids encoding such peptides into recombinant pox viruses using the procedures described in the application. Hence, the specification clearly enables one of skill in the art to make and use the invention.

Working Examples

The Examiner has alleged that the specification provides no working examples because the majority of the examples are directed to tests performed using an animal model (macaques) rather than a human.

First, Applicant submits that the specification fully enables the claimed invention because the Declaration by Dr. Franchini under 37 C.F.R. §1.132 (filed May 16, 2005) and various articles published since the filing of the application show that the invention is effective in humans.

The Declaration by Dr. Genoveffa Franchini describes two clinical trials conducted by Aventis Pasteur as well as proposed clinical trials by EuroVacc. The clinical trials involved administration of a recombinant pox virus that encoded HIV peptides (vCP1452) to human HIV-infected patients. In the ACTG5054 Trial, the patients had been undergoing antiretroviral therapy (ART) and prior to administration of vCP1452 had a median CD4 count of 609 and a viral load of less than 50 (see pages 3 and 5 of the Declaration Appendix). Preliminary results indicated that patients who received the recombinant vCP1452 pox virus alone had a lower viral load than those who received placebo (page 5 of the Declaration Appendix)). In the Quest trial, patients who received the recombinant pox virus had increased CD4 and CD8 responses at week 24 (see page 11 of the Declaration Appendix).

A press release by EuroVacc, which is provided with the Supplemental Information Disclosure Statement filed in May 2005, describes results from a NYVAC-HIV C vaccine trial. *See* article entitled, "Results from EV01 HIV Vaccine Trial, London and Lausanne, July 7th, 2004." The vaccine employed a highly attenuated recombinant vaccinia virus that expresses *gag*, *pol*, *nef* and *env* synthetic genes of HIV-1 clade C. *Id.* As reported, the vaccine was well-tolerated by the 24 people who received it. *Id.* Vaccine-induced anti-HIV T-cell responses were observed in 5/12 (45%) of the vaccine recipients using stringent quality controlled clinical lab assays. *Id.* *Env*-specific responses were found in all 5 responding subjects but additional responses against other proteins of HIV (e.g. Gag and Nef) were detected in 40% of the responders. *Id.* Anti-env antibodies, analyzed at the University of Oxford, were detected in 5/24 (20%) of volunteers at week 4. *Id.* Hence, administration of recombinant pox viruses has beneficial effects.

Moreover, several additional articles listed and provided with the Supplemental Information Disclosure Statement (filed in May 2005) illustrate the efficacy of various HIV vaccines. For example, the article by Jin et al. (J. Virol. 76: 2206-16 (2002)) shows that administration of the ALVAC vCP1452 recombinant virus stimulates an HIV1-specific $CD8^+$ response in HIV-infected patients who have been receiving antiretroviral therapy. Patients included in this study were infected with HIV but had a viral load of 50 copies HIV-1 RNA per ml plasma and an average CD4 count of 779 (see page 2207). As stated at page 2211 of the Jin et al. article, 78% of patients had an increase in $CD8^+$ T-cell responses to at least one HIV-1 antigen (see also Figure 4b and pages 2213-14). The recombinant vCP1452 virus is a recombinant pox virus that encoded gp120, gp41, p55, pol and nef HIV peptides (*id.* at page 2207).

Second, the specification need not contain an example if the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without an undue amount of experimentation. M.P.E.P. § 2164.02. As described above, experiments performed since the filing date of the application show that the invention is effective and can be performed without undue experimentation.

Third, Applicant submits that there are four Examples showing that the invention has successfully been performed in a recognized animal model of HIV-1 infection. As described by

The NIAID Division of AIDS, use of macaque monkeys infected with simian immunodeficiency virus (SIV) comprise a useful animal of model HIV infection because SIV in macaques follows a similar disease course to HIV (The NIAID Division of AIDS, *Animal Models,* http://www.niaid.nih.gov/daids/vaccine/animals.htm (Feb. 10, 2003) (filed in a Supplemental Information Disclosure Statement herewith)).

Therefore, Applicant submits that the specification does provide working examples that do teach how to make and use the invention because the SIV-macaque animal model is a good model of HIV infection in humans and because articles published after the filing date of the application show that the methods described in the specification do successfully stimulate an HIV1-specific $CD8^+$ response in humans.

Vaccine Development Unpredictable

The Examiner has also alleged that HIV vaccine development is unpredictable. Applicant submits that it is irrelevant whether or not HIV vaccine development is unpredictable because the claims are directed to methods for stimulating an HIV1-specific $CD8^+$ response. So long as the method increases the ability of cytotoxic $CD8^+$ T cells to recognize and kill cells expressing foreign (i.e. HIV1) peptides, nothing more is needed.

Thus, Applicant submits that the claimed invention is fully enabled by the specification and respectfully requests withdrawal of this rejection under 35U.S.C. §112, first paragraph.

Conclusion

Applicant respectfully submits that the claims are in condition for allowance, and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney at (516) 795-6820 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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Date November 22, 2005

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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on this 22nd day of November, 2005.

PATRICIA A. HULTMAN

Name

Signature